UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/130,070	12/08/87	WARD D	ENZ-1(CONT)D

EXAMINER
MARSCHEL, A

ART UNIT	PAPER NUMBER
1807	~~19~~ 21

DATE MAILED: 07/23/92

MORGAN & FINNEGAN
345 PARK AVENUE
NEW YORK, NY 10154

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 4/21/92 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☒ Ex'r's Int. Summary, Paper #20

Part II SUMMARY OF ACTION

1. ☒ Claims 104-109, 113-118, 125-137, and 140-144 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 1-103, 110-112, 119-124, 138, 139, and 145 have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 104-109, 113-118, 125-137, and 140-144 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).

12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

Applicants' arguments filed 4/21/92 have been fully considered and they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated from previous office actions or newly applied. They constitute the complete set presently being applied to the instant application.

The Examiner wishes to especially note that none of the amendments to the claims filed 4/21/92 have been entered, nor the addition of new claims, as stated in the letter mailed 7/13/92. This non-entry of said amendment was caused by the improper manner of amending the claims that was attempted in said 4/21/92 amendment. The Examiner additionally wishes to note that only the amendments to the specification have been entered as filed 4/21/92.

The Examiner also notes that the numbering of claims, that were attempted to be added, in the amendment filed 4/21/92 is not accordance with 37 C.F.R. § 1.126. The original numbering of the claims must be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When claims are added, except when presented in accordance with 37 C.F.R. § 1.121(b), they must be renumbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Applicants are hereby reminded that claim 145 was canceled in Paper No. 2, filed 12/8/87, as Preliminary amendment A. Thus

the recent attempt by applicants to start the numbering of newly added claims at 145 is not in accordance with 37 C.F.R. § 1.126.

If applicant desires priority under 35 U.S.C. § 120 based upon a parent application, specific reference to the parent application must be made in the instant application. It is noted that this appears as the first sentence of the specification following the title. Status of all parent applications (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "Patent No." should follow the filing date of the parent application. If a parent application has become abandoned, the expression "abandoned" should follow the filing date of the parent application.

It is especially noted that priority under § 120 is herein only given to include the parent application serial number 06/496,915 because no other applications have been cited as discussed above in this paragraph.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The most distinctive aspect of the present title is the phrase "modified nucleotides" which is so broad that it lacks any significant indication as to what the invention is directed to. Additionally the title is inclusive of three types of invention which are: compositions, methods of making, and methods of using. The instant claims are only directed to methods of using and not to compositions or methods of making them.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by

the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

Claims 105 and 114 are limited to a moiety A that comprises biotin and iminobiotin. There is no enablement in the specification of a moiety A that contains both biotin and iminobiotin within a single A moiety as cited in claims 105 and 114. Similarly, claim 115 discloses a polypeptide comprising avidin, streptavidin, and IgG anti-A immunoglobulin. The specification does not enable such a polypeptide containing all three proteins as cited in claim 115.

Claim 140 was not amended in the claims section of the amendment filed 6/24/91 and was not cancelled due to the non-entry of the amendment filed 4/21/92. Therefore the replacement page for claim 140 that does not contain a "taped on" structure was not entered. Thus, claim 140 with the "taped on" structure remains as claim 140. Correction is required.

Although not clearly depicted in claim 140, the Examiner deems that applicants possibly intend that "H-" be one of the options for "x" as given in claim 140, line 25. There is a lack of any enablement of such a 5'terminus in the instant disclosure.

Claims 140 and 141 cite structures where the "z" moiety is mono-, di-, or tri-phosphate. Such structures completely lack enablement in the instant specification.

Applicants have specifically cited certain genes and/or genetic defects in the instant claims as follows:

Claim 131 cites the penicillin resistance gene of Streptococcus pyrogenes.

Claim 131 cites the penicillin resistance gene of Neisseria meningitidis.

Claim 132 cites the tetracycline resistance gene of Staphylococcus aureus.

Claim 132 cites the tetracycline resistance gene of Candida albicans.

Claim 132 cites the tetracycline resistance gene of Pseudomonas aeruginosa.

Claim 132 cites the tetracycline resistance gene of Streptococcus pyrogenes.

Claim 132 cites the tetracycline resistance gene of Neisseria gonorrhoeae.

Claim 133 cites the aminoglycoside resistance gene of Mycobacterium tuberculosis.

Claim 135 cites the "polynucleotide complementary to the sequence which is absent in thalassemic subjects".

Claim 143 cites α-fetal protein and depends from claim 142 which cites the nucleic acid sequence coding from said protein.

Claim 144 cites carcinoembryonic antigen and depends from claim 142 which cites the nucleic acid sequence coding from said protein.

None of the above listed genes or nucleic acids are enabled

in the instant disclosure. Since they are specifically cited in the claims as listed above they are critical subject matter for the practice of said listed claims.

Claim 141 cites detecting abnormal hormonal receptor sites. The specification lacks any enablement or guidance as to what structures, from those given in claim 140, or detection methods are needed to detect "abnormal" receptor sites. Does someone wishing to detect an abnormal site use an abnormal structure from claim 140? Alternatively, can any structure cited in claim 140 be somehow used to detect abnormal receptor sites? In summary the instant disclosure lacks enablement for the detection method of claim 141 wherein "abnormal" hormonal receptor sites can be detected.

Claims 105, 114, 115, 131-133, 135, 140, 141, 143, and 144 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 104-109, 113-118, 125-137, and 140-144 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to modification of purines (claim moiety B) only at the 7-position of 7-deazapurines or modification of pyrimidines (claim moiety B) at the 5-position. Said modifications are claimed for attachment of moiety A. This rejection is directed to the non-enablement of the C-8 purine modification. It is noted that applicants cite mercuration at the only method of initiating said modifications of nucleotide bases. On page 3, lines 6-28, of the specification mercuration

is discussed wherein Dale et al.(1973) and Dale et al.(1975a) are cited as to C-5 pyrimidine, C-8 purine, and C-7 deazapurine mercuration. These references are enclosed herewith. No other references or methodology are instantly disclosed to support other base modification methods. Review of the Dale et al. references reveals a lack of support for the C-8 purine modification by mercuration. For example, the abstract of Dale et al.(1973) only cites C-5 pyrimidine and C-7 deazapurine modification. On page 2239, second column, lines 11-14, three sites of modification are suggested (without factual evidence for C-8 purine modification) and then in lines 22-24 the structures of Figure 1 are described as being produced. It is noted that Figure 1 only shows C-5 pyrimidine and C-7 deazapurine modification. The lack of a C-8 purine structure is hereby noted. The only other C-8 purine discussion is on page 2241, second column, in the first sentence of the "DISCUSSION" section. This assertion of C-8 purine modification lacks factual support as to its being prepared as pointed out in the above discussion relating to Figure 1 in the reference by Dale et al.(1973) and therefore lacks enabling support for the instantly claimed C-8 purine modification practice. The other Dale et al.(1975a) reference does not cure this lack of enablement. The abstract of Dale et al.(1975a) does not described C-8 purine modification. On page 2455, first column, lines 31-37, a minor product that <u>may</u> be 8-mercuri-GMP is cited but was not characterized as admitted therein. Such a speculative assignment of structure clearly

lacks the disclosure to support the requirement of clear and concise enablement. The accompanying reference by Dale et al.(1975b) discloses only C-5 pyrimidine practice. In summary the scope of the instant enablement does not include C-8 purine modification. See M.P.E.P. §§ 706.03(n) and 706.03(z).

Claims 104-109, 113-118, 125-137, and 140-144 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 113 is vague and indefinite in that the polypeptide complexing practice therein claimed is unclear. Since the polypeptide is cited as forming a complex with a compound in accordance with claim 125, it is unclear whether the complex formation is mediated by moiety A or whether the polypeptide can bind anywhere on the compound of claim 125 without specifically binding to moiety A. Which is meant by the complex formation practice of claim 113? Clarification of the claim wording is requested to clarify what complex formation is meant to be claimed with regard to the cited polypeptide.

The structure of claim 125 is vague and indefinite because the third ribose moiety lacks the "z" group at the 2' position as compared to the other riboses that are depicted. Correction of this conflict is requested.

Claim 140 cites the moiety "H-HO-" as one of the represented options for "x, y, or z". This structure is vague and indefinite as to what is meant.

In claims 126, 128, 130, 134, 135, and 142; lines 3, 11, 3-4, 3, 3, and 3; respectively; the target is cited as being a "nucleic acid sequence". This is vague and indefinite since a "nucleic acid sequence" is a mathematical representation of a polynucleotide and not a composition. How can a target be a mathematical representation? This type of vague and indefinite citation is present in several other citations also wherein the word "sequence" is used to describe a nucleic acid composition. Clarification of the claim language is requested.

Claim 140 is vague and indefinite in that a "cyclic moiety" is cited in line 28, followed by a depiction of a structure which is not cyclic. Clarification of this conflict is requested.

Claim 140 cites "said compound having the structure" in lines 4-7. This conflicts with the compound defined in claim 125 from which claim 140 depends. The conflict is caused by the definition of a compound in claim 140 given by the structure shown in line 7 of claim 140 which is different from said compound from claim 125 which is a polymer. Clarification is requested as what is meant by said compound in line 4 of claim 140.

Claims 108 and 117 are rejected under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Claims 108 and 117 are limited to A being a ligand. This is not further limiting from claims 104 and 113, respectively, since the complexing practice of claims 104 and 113 is apparently via

binding to moiety A. Such binding can only occur if A is a ligand that can participate is said binding. It is noted that the wording of claim 113 is rejected above as being unclear as to what portion of the compound of claim 125 that the polypeptide complexes with.

35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 141-144 are rejected under 35 U.S.C. § 101 because there is no evidence given in the instant disclosure that supports the diagnostic utility claimed as detecting malignant cells (claim 141) or diagnosing a tumor cell (claims 142-144). Such diagnostic utility must be supported by evidence that supports definite and currently available utility.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 125-127 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Langer et al.

The disclosure of Langer et al. reads on the above rejected claims via the detection of hybridized biotinylated probe to E.

coli DNA as shown on page 6636 in Figure 2 and discussed in the Figure 2 legend. The chemical structure on page 6633, second column, discloses the C-5 pyrimidine biotinylation moiety. The author list of Langer et al. is the same as the inventor list of the instant application but has been published more than a year before the filing date of serial number 06/496,915. This reference is applicable because priority has not been given prior to serial number 06/496,915 as discussed above with regard to 35 U.S.C. § 120.

The disclosure is objected to because of the following informalities:

On page 38, line 10, the word "immunfluorescent" appears to be misspelled.

On page 47, line 20, the word "chromotographic" appears to be misspelled.

In line 5 of claim 136 the word "seqeunces" appears to be misspelled.

Appropriate correction is required.

Claims 104-109, 113-118, 128-137, and 140-144 are allowable over the prior art of record because the prior art of record does not teach or suggest the instantly claimed methods of use for compositions having the specific points of attachment to the nucleoside residue bases of moiety A.

No claim is allowed.

The Examiner reiterates from the last page of the previous office action mailed 10/21/91 that none of the references cited

in the parent application serial number 06/496,915 or cited on PTO Form 1449 filed 8/7/89 in the instant application have been considered in the instant application because of a continued lack of access to said parent application as well as a lack of copies of the cited references filed in the instant application. Thus the Examiner cannot fulfill the previous request of applicants to consider and make of record those references in the instant application. The Examiner suggests that applicants send copies of any references that applicants wish to have considered in the instant application along with an appropriate PTO Form 1449.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

The CM1 Fax Center number is (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ardin Marschel, Ph.D., whose telephone number is (703) 308-3894.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

AM

A. MARSCHEL:am

July 21, 1992

M. Moskowitz

MARGARET MOSKOWITZ
SUPERVISORY PATENT EXAMINER
GROUP 180